MINISTRY OF HEALTH AND PREVENTION

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Comments on Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC.

The Danish Ministry of Health and Prevention welcomes the Commissions consultation document on the functioning of the clinical trials directive. We support the initiative of the Commission to improve the functioning of the directive and remedy shortcomings of the regulatory framework and we believe that the consultation document presents many good initiatives.

From a Danish perspective, the consultation document gives rise to the following comments on key issues.

Streamlining the procedures
The Danish Ministry of Health and Prevention supports the idea of a community procedure for multinational clinical trials. The national procedures are burdensome for the sponsors and it may impede the development of new pharmaceuticals or lead to multinational clinical trials being moved to other parts of the world.

There is a need for harmonisation of application procedures for multinational clinical trials. We emphasise the significance of a mechanism whereby the Member States concerned are obliged to try to reach a common decision as regards a clinical trial involving different Member States.

The new procedure could be inspired by experiences with the decentralised procedure for marketing authorisations and the voluntary harmonisation procedure. The assessment should be prepared by a reference member state and be applicable for the clinical trial in all Member States concerned, but the authorisation decision should be issued by the NCAs individually. Therefore, if a similar procedure to the decentralised one is introduced, it is important to bear in mind that a coordination group equivalent to the CMD(h) would be needed and a clear decision making procedure should be established. The same accounts for the possibility for a member state to appeal or reject a decision made by the reference member state in case of disagreements.

With regard to amendments and follow-ups on safety issues it would be preferable if assessment of such is prepared by the reference member state in cases where the clinical trial involves several Member States.

The Danish Ministry of Health and Prevention agrees that ethical issues fall within the ambit of Member States and should remain therein.

This opinion does not exclude the possibility to streamline the procedure for the overall functioning of the Ethics Committees. It seems to be a very challenging task to achieve real streamlining of the procedures for multinational clinical trials without improvements of the procedures in relation to the Ethics Committees.

Therefore, it should be considered how the cooperation between national Ethics Committees could be improved. One suggestion could be a one-stop shop of submission of the assessment dossier, and strengthening of networks of national Ethics Committees involved in multinational clinical trials, as suggested by the Commission. Better cooperation between Ethics Committees could also be supported by web-based technologies and direct access to each others assessments and best practice. Such approach would not interfere with member states ethics considerations.

Reporting of SUSARs and the annual safety report
The Danish Ministry of Health and Prevention finds that the rules on reporting of SUSARs could be simplified. Sponsor should only report a SUSAR to the NCA in the Member State where it has occurred, and the NCA should make sure that the SUSAR is reported to the Eudravigilance Database and the other Member States concerned. The Eudravigilance Database should provide an automatic and simultaneous transmission of the SUSAR to the other Member States concerned. In the future the database search facilities should be improved and community procedures for signal detection should be established.

It seems superfluous that the sponsor shall report SUSARs to the Ethics Committee(s). The NCA is responsible for the monitoring and has the competence to suspend or prohibit a clinical trial according to article 12 of the clinical trials directive. The NCA shall inform the Ethics Committee concerned of its decision. In Denmark the Ethics Committees are not involved in the monitoring of the clinical trials.

As for the annual report of the trial subjects´ safety it is an important document for NCA's in order to ensure that the safety and well-being of trial subjects are protected. The Danish Ministry of Health and Prevention suggests that the content of the safety report is being regulated and that the report should be provided quarterly to the NCA. In addition, it should be possible for the NCA to demand a safety report whenever it finds it necessary. It is an unnecessary administrative burden that the sponsor shall send safety reports to the Ethics Committee(s) which is not responsible for the monitoring of the trial.

The scope of the directive and requirements in relation to clinical trials.
The Danish Ministry of Health and Prevention finds that the scope of the clinical trials directive should continue to encompass all kinds of clinical trials, including the clinical trials performed by "academic" sponsors. This is due to the fact that the Clinical Trials Directive establishes specific provisions regarding the conduct of clinical trials in order

to ensure that good clinical practice is followed. Compliance with the good clinical practice provides assurance that the rights, safety and well-being of trial subjects are protected and that the results of the clinical trials are credible.

The Danish Ministry of Health and Prevention agrees that the legal requirements according to the directive should differentiate on a risk-based approach. The clinical trials are very varied and the actual risk for the participants depends on a range of different factors as mentioned by the Commission. A risk-based approach should take into account the various phases and types of clinical trials and the different kinds of investigational medicinal products.

The Danish Ministry of Health and Prevention also finds that the delimitation between clinical trials (interventional trials) and non-interventional trials is very difficult in some cases. As it is very important to know whether a study shall or not shall be conducted in accordance with GCP we find that any new regulation must solve this problem.

Substantial amendments
The Danish Ministry of Health and Prevention finds that the definition of substantial amendments needs to be revised and simplified. It is too broad and open for various interpretations. We suggest a clear definition with a positive enumeration of the different types of amendments or a positive definition without an open end.

Furthermore The Danish Ministry of Health and Prevention suggests a timeline for assessment of substantial amendments by the NCA. The timeline should be identical to the timeline for the Ethics Committee.

Clarifying the respective scope of assessment of NCA and Ethics Committees
The Danish Ministry of Health and Prevention supports initiatives to clarify the respective scope of assessment by NCAs and Ethics Committees, which can contribute to a clearer identification of their respective roles and responsibilities and avoid overlaps. It could be considered whether it is suitable that both the NCA and Ethic Committee individually shall evaluate the content of investigators brochure, including a compilation of clinical and non-clinical data on the investigational medicinal product, and the anticipated therapeutic benefits compared to the risks. Some of the new investigational medicinal products are very complicated and they require special expertise to evaluate the benefit-risk. To some extent it might be useful to facilitate cooperation between the NCA and Ethics Committees within the legal framework in this field.

Emergency clinical trials
The issue of emergency clinical trials is much debated in Denmark. In order to give patients the best possible treatment it is essential that there is evidence for the effect of treatments. For some groups of patients this requires that the treatment is tested in emergency situations.

From a Danish point of view it is very important that the issue of conducting clinical trials in emergency situations is addressed and that the directive is revised in order to create better possibilities to perform emergency clinical trials.

In the spring 2009 the Danish Minister for Health and Prevention appointed a committee, which will review the Danish Biomedical Research Ethics Committee System. The

committee will mainly focus on the structure and organisation of the system, aiming to strengthen the system by efficient management as well as focusing on the issue of supervision and quality management. The report, which is expected to be published within weeks, will also address the question of emergency clinical trials. When the report is published I will send the Commission an abstract of the report with its recommendations. I will at the same time elaborate the Danish views regarding clinical trials in emergency situations.

The Danish Ministry of Health and Prevention looks forward to discussing the Commissions proposal on new rules on clinical trials later during the process.

Yours sincerely

Dorthe Eberhardt Søndergaard
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